Structural Modifications of Strigol Analogues. Influence of the B and C Rings on the Bioactivity of the Germination Stimulant GR24

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Several analogues of GR24 with modifications in the ABC part of the molecule were prepared from simple esters and lactones by α-formylation followed by coupling with a bromofuranone. The α-formyl derivative of 2-coumaranone was prepared in good yield via the corresponding α-ethoxymethylene compound. Evaluation of the biological activity of the new analogues lacking ring B and/or C revealed that the ABC part of the GR24 molecule is not essential for germination stimulation of *Striga* and *Orobanche* seeds. Variation in the position of ring A with respect to ring D had a considerable influence on the biological activity. The derivative of 2-coumaranone was completely inactive. A simple analogue derived from γ-phenyl-γ-butyrolactone was almost as active as GR24 itself.

INTRODUCTION

Parasitic weeds belonging to the genera *Striga* and *Orobanche* directly affect the lives of more than 400 million people in Africa, Asia, and the Middle East by severely reducing the yields of graminaceous and leguminous crops (Musselman, 1987; Parker, 1986; Ramaiah, 1987). *Striga* species, commonly known as "witchweed", particularly affect sorghum, millet, maize, rice, and sugar cane. *Orobanche* species, whose common name is "broomrape", affect sunflower, tomato, tobacco, lentils, broad beans, and many other crops. The parasitic process begins with the germination of the seeds of the weeds induced by a stimulant which is present in the root exudate of the host plant (Brown, 1965). Strigol 1 is a naturally occurring germination stimulant that has been isolated from the root exudate of cotton (*Gossypium hirsutum* L.) and has been chemically characterized by Cook et al. (1966, 1972). The detailed chemical structure including its absolute configuration was established several years after it was first isolated (Brooks et al., 1985). This natural stimulant can be used to design a herbicide for the control of weed pests by means of the so-called suicidal germination methodology (Eplee, 1975), i.e., introduction of a germinating agent into the soil to induce germination of the parasitic weed seeds before the desired crops are planted. In the absence of a host the germinated seeds cannot develop further and consequently will die.

Strigol itself is too complicated a molecule for this purpose; its synthesis would be lengthy and uneconomical. Therefore, considerable effort has been put into the development of analogues of strigol, which have a simpler structure but which have retained an appreciable biological activity. In particular, Johnson et al. (1976, 1981) synthesized and biologically evaluated a series of strigol analogues, of which compounds **2** (GR24), **3** (GR18), **4** (GR7), and **5** (GR5) are the most active (Figure 1). Although no systematic structure–activity relationship study has been carried out, the results obtained so far strongly suggest that the actiphore, i.e., the part of the strigol molecule which is primarily responsible for the bioactivity, resides in the CD moiety of the strigol molecule (Hassanali, 1984; Mangnus and Zwanenburg, 1991). In this paper further modifications of strigol have been investigated and tested for biological activity.

MATERIALS AND METHODS

Nomenclature. We have adopted Chemical Abstracts Service nomenclature for all compounds; ring D is named as a *dihydrofuranone*. In the older literature the name *butenolide* is used for this fragment, which has consequences for the atom numbering.

Synthesis. *General Remarks.* Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM390 (90 MHz) spectrometer with TMS as internal standard. For mass spectroscopy a double-focusing VG 7070E was used. Flash chromatography was carried out at a pressure of ca. 1.5 bar using silica gel 60H (Merck art. no. 7719). Thin-layer chromatograms (TLC) were run on plastic-supported silica gel 60 plates (0.2-mm layer, F_{254}, Merck art. no. 5735) or glass-supported silica gel 60 plates (0.25-mm layer, F_{254}, Merck art. no. 5715).

Solvents were dried using the following methods: Dimethylformamide P.A. was dried on 4-Å molecular sieves. Tetrahydrofuran was distilled from lithium aluminum hydride just before use. Petroleum ether 60–80 and hexane were distilled from calcium hydride. Diethyl ether was predried over calcium chloride and then distilled from sodium hydride. Dichloromethane was distilled from phosphorus pentoxide. All other solvents used were of either P.A. or "reinst" quality.

Pure sodium hydride was obtained from a 60% dispersion in mineral oil by washing the dispersion several times with anhydrous hexane to remove the oil. To exclude contact of the sodium hydride with moist air, the washings were carried out in a continuous stream of dry nitrogen.

The syntheses of 5-bromo-3-methyl-2(5*H*)-furanone (**18**) (Scheme III, L = Br), 3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one (**20**) (Scheme IV), and 3-(hydroxymethylene)-3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one (**22**) (Scheme IV) have been described by Johnson et al. (1981). For an improved preparation of these three compounds, see Mangnus et al. (1992a).

Methyl 2-Indanylacetate (**21**). A solution of 3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one (**20**) (1.04 g, 6 mmol) in methanol (25 mL) was subjected to hydrogenolysis for 2 h with Pd(C) as the catalyst. The catalyst was filtered off and the filtrate concentrated in vacuo. *2-Indanylacetic acid* (1.04 g, 98%) was obtained as a white solid: mp 87.0–90.5 °C [lit. mp 91–92 °C (Groves and Swan, 1951)]; ^{1}H NMR ($CDCl_3$) δ 2.40–3.33 (m, 7 H), 7.10 (s, 4 Ar *H*), 10.32 (br s, O*H*); IR (KBr) ν 3300–2400 (COOH), 1685 (COOH) cm^{-1}.

Thionyl chloride (0.73 mL, 0.01 mol) was gradually added to methanol (P.A., 10 mL) with stirring at −30 °C. Then a solution of crude 2-indanylacetic acid (0.88 g, 0.005 mol) in methanol (5 mL) was gradually added. The mixture was allowed to warm slowly to room temperature and stirred overnight. Methanol

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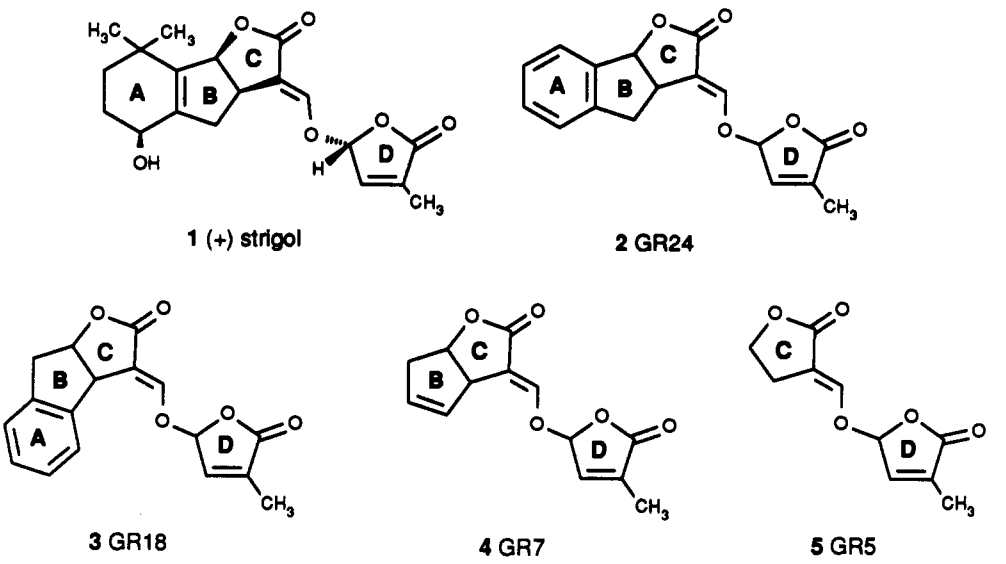


Figure 1. Strigol and some active analogues.

and other volatile compounds were removed in vacuo, and the residue was dissolved in diethyl ether. The ether solution was extracted with saturated aqueous sodium carbonate, dried ($MgSO_4$), filtered, and concentrated. The methyl ester **21** (0.94 g, 99%) was obtained as a colorless oil which solidified on standing: ^{1}H NMR ($CDCl_3$) δ 2.38–3.30 (m, 7 H), 3.67 (s, 3 H, OCH_3), 7.18 (br s, 4 Ar *H*).

Methyl 2-(Hydroxymethylene)-2-indanylacetate (**25**). Pyridinium tosylate (0.50 g, 1.0 mmol) was added to a mixture of 3-(hydroxymethylene)-3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one (**22**) (2.01 g, 10 mmol) and ethyl vinyl ether (4.50 g, 62 mmol) in dichloromethane (75 mL) with stirring at 0 °C under nitrogen. The mixture was stirred for 3 h at 0 °C and stored overnight in a refrigerator. The reaction mixture was extracted with saturated aqueous sodium chloride, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; diethyl ether/hexane 2:1) to afford *3-[[(1-ethoxyethyl)oxy]methylene]-3,3a,4,8b-tetrahydroindeno[1,2-b]furan-2-one* (**23**) as a viscous, colorless oil (1.94 g, 71%): ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7 Hz, 3 H, CH_3), 1.46 (d, J = 5.5 Hz, 3 H, CH_3), 2.86–4.04 (m, 5 H, OCH_2CH_3 + H_{3a} + 2 × H_4), 5.12 (q, J = 5.5 Hz, OC*H*O), 5.86 (d, J = 7.5 Hz, H_{8b}), 7.04–7.77 (m, 4 Ar *H* + =C*H*O).

The ethoxyethyl ether **23** (0.69 g, 2.5 mmol) was dissolved in methanol (25 mL) and subjected to hydrogenolysis for 1.5 h with Pd(C) as the catalyst. Then the catalyst was filtered off, and the filtrate was treated with excess diazomethane. After 1 h of stirring at room temperature, excess diazomethane was removed and the solution was concentrated in vacuo. The residue was purified by flash chromatography (silica gel; dichloromethane) to afford *methyl 2-[[(1-ethoxyethyl)oxy]methylene]-2-indanylacetate* (**24**) as a colorless oil (0.33 g, 46%): ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7 Hz, 3 H, CH_3), 1.33 (d, J = 5.5 Hz, 3 H, CH_3), 2.71–3.73 (m, 7 H, OCH_2CH_3 + $ArCH_2CHCH_2Ar$), 3.62 (s, OCH_3), 4.96 (q, J = 5.5 Hz, OC*H*O), 7.05 (s, 4 Ar *H*), 7.61 (s, =C*H*O); IR (CCl_4) ν 1710 (C=O, ester), 1640 (C=C, enol ether) cm^{-1}.

A mixture of ester **24** (0.29 g, 1 mmol) in tetrahydrofuran (5 mL) and 0.5 N aqueous hydrogen chloride was stirred at room temperature for 20 h. Stirring was continued at 55 °C for another 24 h. After cooling to room temperature, the aqueous layer was saturated with sodium chloride and extracted with diethyl ether (3×). The combined organic layers were extracted with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated. The crude product (0.213 g, 98%) was obtained as a light brown oil (hydroxymethylene compound **25**) which was sufficiently pure for further use: ^{1}H NMR ($CDCl_3$) δ (mixture of keto and enol forms) 2.39–3.80 (m, 5 H, $ArCH_2CHCH_2Ar$ and α-H keto form), 3.59 (s, OCH_3 keto form), 3.66 (s, OCH_3 enol form), 7.07 (s, 4 Ar *H*), 7.63 (s, =C*H*O enol form), 8.29 (d, J = 3 Hz, C*H*=O keto form).

Methyl 2-Indanyl-2-[[(2,5-dihydro-4-methyl-5-oxo-2-furanyl)oxy]methylene]acetate (**6**). A solution of crude hydroxymethylene compound **25** (0.213 g, ca. 1 mmol) in dimethylformamide (10 mL) was added to a solution of potassium *tert*-butoxide (0.112 g, 1 mmol) in dimethylformamide (5 mL) with stirring at 10 °C under nitrogen. Then the solution was cooled to −60 °C, and 5-bromo-3-methyl-2(5*H*)-furanone (**18**) (L = Br; 0.20 g, 1 mmol) in dimethylformamide (5 mL) was gradually added. The mixture was allowed to warm to room temperature and stirred for 16 h. Dimethylformamide was removed in vacuo, and the residue was dissolved in saturated aqueous ammonium chloride and dichloromethane. The aqueous layer was extracted with dichloromethane (3×), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product (brown oil) was purified by flash chromatography (silica gel; hexane/ethyl acetate 5:2) to afford **6** (0.163 g, 52% based on **23**) as a yellow oil in addition to some starting material **25** (0.08 g, 41%). The product was dissolved in a very small amount of hot diisopropyl ether, and after cooling, the colorless crystals of **6** were filtered off: mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (m, 3 H, CH_3), 2.67–3.79 (m, 5 H, $ArCH_2CHCH_2Ar$), 3.64 (s, 3 H, OCH_3), 5.95 (m, OC*H*O), 6.68 (m, =C*H*C), 7.04 (s, 4 Ar *H*), 7.46 (m, =C*H*O); IR (CCl_4) ν 1795 (C=O, furanone), 1715 (C=O, ester), 1645 (C=C, enol ether) cm^{-1}; MS (EI$^+$) 314 (M)$^+$, 282 (M − CH_3OH)$^+$, 217 (M − furanone)$^+$, 185 [100%, (M − furanone − CH_3OH)$^+$], 97 [100%, (furanone)$^+$]. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.65; H, 5.83.

Dihydro-3-[[(2,5-dihydro-4-methyl-5-oxo-2-furanyl)oxy]methylene]-5-phenyl-2(3H)-furanone (**7**). Potassium *tert*-butoxide (2.50 g, 24 mmol) was added in small quantities to a solution of dihydro-5-phenyl-2(3*H*)-furanone (**16**) (R = Ph, R′ = H; 3.24 g, 20 mmol; purchased from Jansen Chimica) and methyl formate (1.80 mL, 20 mmol) in tetrahydrofuran (50 mL) with stirring at 0 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 18 h. Then the mixture was cooled to −60 °C, and 5-bromo-3-methyl-2(5*H*)-furanone (**18**) (L = Br; 3.60 g, 21 mmol) was gradually added. The mixture was brought to room temperature and stirred for 4 h. Tetrahydrofuran was removed in vacuo, and the residue was dissolved in dichloromethane and treated with saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product (brown/yellow oil) was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate 3:2) and afforded two partly separated diastereomers of **7**: yield 70%; ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 3 H, CH_3), 2.62–3.54 (m, 2 H, CH_2), 5.38–5.64 (m, C*H*Ph), 6.17 (m, OC*H*O), 6.92 (m, =C*H*C), 7.18–7.62 (m, 5 H, 4 Ar *H* + =C*H*O); IR (CCl_4) ν 1800 (C=O, 4-methylfuranone), 1770 (C=O, lactone), 1690 (C=C, enol ether) cm^{-1}; MS (CI$^+$) 287 (M + 1)$^+$, 190 (M − 4-methylfuranone)$^+$, 97 [100%, (4-methylfuranone)$^+$]. Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.86; H, 5.04.

The pure fast moving diastereomer was obtained as a white

solid and could be recrystallized from ethyl acetate/hexane: mp 150–152 °C. Pure slow moving diastereomer was obtained as a yellow oil, which failed to crystallize.

Methyl 2-[[(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)oxy]-methylene]-4-phenylbutanoate (8). For the preparation of analogue 8 from methyl 4-phenylbutanoate the procedure described for 7 was followed. The crude product (brown oil) was purified by flash chromatography (silica gel; hexane/ethyl acetate 3:1) to afford pure 8 (0.160 g, 11%), recovered starting ester (0.555 g, 62%), and furanone 18 (L = Br; 0.260 g). Analogue 8 was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 3 H, CH_3), 2.30–2.81 (m, 4 H, CH_2CH_2), 3.69 (s, 3 H, OCH_3), 5.86 (m, OC*H*O), 6.63 (m, =C*H*C), 7.15 (s, 5 Ar *H*), 7.40 (s, =C*H*O); IR (CCl_4) ν 1795 (C=O, furanone), 1715 (C=O, ester), 1655 (C=C, enol ether) cm^{-1}; MS (EI$^+$) 302 (M)$^+$, 271 (M – CH_3O)$^+$, 205 (M – furanone)$^+$, 97 [100%, (furanone)$^+$], 91 [100%, ($PhCH_2$)$^+$]. Peak match calcd for $C_{17}H_{18}O_5$: 302.1154. Found: 302.1150.

Dihydro-3-[[(2,5-dihydro-4-methyl-5-oxo-2-furanyl)oxy]-methylene]-4-phenyl-2(3H)-furanone (13). Potassium *tert*-butoxide (1.93 g, 17 mmol) was added in small quantities to a solution of dihydro-4-phenyl-2(3*H*)-furanone (16) [R = H, R′ = Ph (De Puy et al., 1964); 2.43 g, 15 mmol] and methyl formate (1.20 g, 20 mmol) in tetrahydrofuran (10 mL) with stirring at 0 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 18 h. Then tetrahydrofuran was removed in vacuo, and the residue was dissolved in water and brought to pH 2 with 1 N aqueous hydrogen chloride. The aqueous solution was extracted with ethyl acetate (3×). The combined organic layers were extracted with saturated aqueous sodium chloride, dried (Na_2SO_4), filtered, and concentrated. The crude product (yellow solid) was purified by recrystallization from ethyl acetate/petroleum ether to give *dihydro-3-(hydroxymethylene)-4-phenyl-2(3H)-furanone* (17) (R = H, R′ = Ph, M = H; 1.77 g, 62%) as pale yellow crystals: mp 123–126 °C; ^{1}H NMR (CD_3OD) δ 3.24–3.68 (m, C*H*Ph), 4.71–4.84 (m, 2 H, CCH_2O), 7.08–7.41 (m, 5 Ar *H*), 7.68 (m, =C*H*O).

For the coupling of hydroxymethylene 17 (R = H, R′ = Ph, M = H) with furanone 18 (L = Br) the procedure described for 6 was followed. The crude product (brown oil) was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate 3:2) to afford two partly separated diastereomers of 13: yield 64%; ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 3 H, CH_3), 4.14–4.81 (m, 3 H, PhC*H*CH_2O), 5.98 (m, OC*H*O), 6.65 (m, =C*H*C), 7.08–7.42 (m, 5 Ar *H*), 7.57 (m, =C*H*O); IR (KBr) ν 1770 (C=O, 4-methylfuranone), 1735 (C=O, lactone), 1670 (C=C, enol ether) cm^{-1}; MS (CI$^+$) 287 (M + 1)$^+$, 190 (M + 1 – 4-methylfuranone)$^+$, 173 (M – 4-methyl-2-oxyfuranone)$^+$, 97 [100%, (4-methylfuranone)$^+$]. Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.28; H, 4.93. Small samples of pure diastereomers were recrystallized from ethyl acetate/hexane. Fast moving diastereomer: white crystals, mp 96–98 °C. Slow moving diastereomer: white crystals, mp 154–156 °C. As was observed for GR7 (Mangnus and Zwanenburg, 1992) and GR24 (Mangnus et al., 1992a), the analytical data, except the melting points, are the same for both diastereomers.

Methyl 3-Phenyl-2-[[(2,5-dihydro-4-methyl-5-oxo-2-furanyl)oxy]methylene]propanoate (9). A solution of potassium *tert*-butoxide (1.12 g, 10 mmol) in tetrahydrofuran (15 mL) was gradually added to a solution of methyl 3-phenylpropanoate (1.64 g, 10 mmol) and methyl formate (0.9 mL; 15 mmol) in tetrahydrofuran (10 mL) with stirring at 0 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 18 h. Tetrahydrofuran was removed in vacuo, and the residue was dissolved in diethyl ether and saturated aqueous sodium carbonate. The aqueous layer was extracted with diethyl ether (2×), brought to pH 3 with 1 N aqueous hydrogen chloride, and extracted with dichloromethane (3×). The combined dichloromethane layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified with flash chromatography (silica gel; chloroform) to give *methyl 2-(hydroxymethylene)-3-phenylpropanoate* (0.59 g, 31%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ mixture of keto and enol tautomers 2.85–3.68 [m, 2 H, CH_2 and C(O)C*H*C(O) keto form], 3.63 (s, 3 H, OCH_3), 6.88–7.33 (m, 5 Ar *H* and =C*H*O enol form), 9.66 (m, C*H*O), 11.48–11.63 (m, O*H* enol).

For the coupling of the methyl 2-(hydroxymethylene)-3-phenylpropanoate with furanone 18 (L = Br) the procedure described for 6 was followed. The crude product was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate 4:1 → 2:1) to afford 9 as a pale yellow oil: yield 73%; ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 3 H, CH_3), 3.54 (s, 2 H, CH_2), 3.62 (s, 3 H, OCH_3), 6.04 (m, OC*H*O), 6.47 (=C*H*C), 7.14 (s, 5 Ar *H*), 7.53 (s, =C*H*O); IR (CCl_4) ν 1795 (C=O, furanone), 1720 (C=O, ester), 1655 (C=C, enol ether) cm^{-1}; MS (EI$^+$) 288 (M)$^+$, 257 (M – OCH_3)$^+$, 191 (M – furanone)$^+$, 97 [100%, (furanone)$^+$], 91 ($PhCH_2$)$^+$. Peak match calcd for $C_{16}H_{16}O_5$: 288.0998. Found: 288.0998.

Methyl 2-[[(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)oxy]-methylene]phenylacetate (10). For the preparation of analogue 10 from methyl phenylacetate the procedure described for 7 was followed. The crude product (yellow oil) was purified by recrystallization from diisopropyl ether. Compound 10 was obtained as colorless crystals: yield 68%; mp 88–89 °C; ^{1}H NMR ($CDCl_3$) δ 1.87 (m, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 6.06 (m, OC*H*O), 6.76 (m, =C*H*C), 7.27 (s, 5 Ar *H*), 7.70 (s, =C*H*O); IR (KBr) ν 1770 (C=O, furanone), 1705 (C=O, ester), 1640 (C=C, enol ether) cm^{-1}, MS (EI$^+$) 274 (M)$^+$, 177 (M – furanone)$^+$, 145 (M – furanone – CH_3OH)$^+$, 97 [100%, (furanone)$^+$]. Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.94; H, 5.17.

Methyl 2-[[(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)oxy]-methylene]-4-chlorophenylacetate (11). For the preparation of analogue 11 from methyl 4-chlorophenylacetate the procedure described for 7 was followed. The crude product was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate 2:1) followed by recrystallization from diisopropyl ether to afford 11 as white needles: yield 58%; mp 97–97 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (m, CH_3), 3.75 (s, OCH_3), 6.13 (m, OCHO), 6.85 (m, =CHC), 7.00–7.50 (AB quartet, J_{AB} = 9.0 Hz, 4 Ar H), 7.73 (s, =CHO); IR (KBr) ν 1785 (C=O, furanone), 1710 (C=O, ester), 1630 (C=C, enol ether), 830 (para-substituted aromatic) cm^{-1}; MS (CI$^+$) 309/311 (M + 1)$^+$, 277/279 (M = CH_3OH)$^+$, 211/213 (M – furanone)$^+$, 97 [100%, (furanone)$^+$]. Anal. Calcd for $C_{15}H_{13}ClO_5$: C, 58.36; H, 4.24. Found: C, 58.17; H, 4.25.

Methyl 2-[[(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)oxy]-methylene]-4-methoxyphenylacetate (12). For the preparation of analogue 12 from methyl 4-methoxyphenylacetate the procedure described for 7 was followed. The crude product was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate 2:1) to afford pure 12 as a viscous yellow oil: yield 82%; ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 3 H, CH_3), 3.72 (s, 2 H, OCH_3), 6.07 (m, OC*H*O), 6.79 (m, =C*H*C), 6.50–7.50 (AB quartet, J_{AB} = 9.9 Hz, 4 Ar *H*), 7.65 (s, =C*H*O); IR (KBr) ν 1775 (C=O, furanone), 1710 (C=O, ester), 1635 (C=C, enol ether), 840 (para-substituted aromatic) cm^{-1}; MS (EI$^+$) 304 (M)$^+$, 207 [100%, (M – furanone)$^+$]. Peak match calcd for $C_{16}H_{16}O_6$: 304.0947. Found: 304.0938.

3-(Ethoxymethylene)-2(3H)-benzofuranone (28). A mixture of 2(3*H*)-benzofuranone (26) (3.35 g, 25 mmol), triethyl orthoformate (6.70 g, 45 mmol), and acetic anhydride (6.65 g, 65 mmol) was stirred for 1 h at 120 °C and then for 1 h at 140 °C. The reaction vessel was equipped with a small condensor to allow evaporation of formed ethanol. After cooling, acetic anhydride and excess triethyl orthoformate were removed in vacuo, and the residue was dissolved in hot 2-propanol. After cooling of the 2-propanol solution, product 28 crystallized as light brown needles: yield 92%; mp 101–102 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (t, J = 7 Hz, 3 H, CH_3), 4.29 (q, J = 7 Hz, 2 H, OCH_2C), 6.92–7.32 (m, 3 Ar *H*), 7.46–7.69 (m, 2 H, 1 Ar*H* + =C*H*O); IR (KBr) ν 1760 (C=O, lactone), 1655 (C=C, enol ether) cm^{-1}; MS (EI$^+$) 190 (M)$^+$, 162 [100%, (M – C_2H_4)$^+$], 134 (M – C_2H_4 – CO)$^+$. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30. Found: C, 69.51; H, 5.39.

3-(Hydroxymethylene)-2(3H)-benzofuranone (29). A solution of benzofuranone 28 (1.78 g, 9.37 mmol) in a mixture of concentrated acetic acid (5 mL) and concentrated aqueous hydrogen chloride (5 mL) was stirred at room temperature for 2 days. The precipitated product was then filtered off and washed with water. The wet solid was dissolved in ethyl acetate, and the solution was dried (Na_2SO_4), filtered, and concentrated. The crude product was recrystallized from toluene to afford 29 as light gray crystals (1.00 g, 66%): mp 163–168 °C [lit. 169 °C (Chatterjea, 1960)]; ^{1}H NMR (DMSO-d_6) δ 6.95–7.32 (m, 3 Ar *H*), 7.51–7.76 (m, 1 Ar *H*), 7.96 (s, =C*H*O).

3-[[(2,5-Dihydro-4-methyl-5-oxo-2-furanyl)oxy]methylene]-2-benzofuranone (14). For the reaction of hydroxymethylene compound **29** with 5-bromo-3-methyl-2(5*H*)-furanone (18) (L = Br) the procedure described for **6** was followed. The crude product was purified by flash chromatography (silica gel; ethyl acetate/petroleum ether 1:1) followed by recrystallization from 2-propanol to afford **14** as a yellow solid: yield 0.254 g (16%); mp 131–139 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (m, 3 H, CH_3), 6.34 (m, OC*H*O), 7.05–7.15 (m, 3 Ar *H*), 7.26–7.32 (m, 1 Ar *H*), 7.55 (m, =C*H*C), 7.73 (s, =C*H*O); IR (KBr) ν 1780 (C=O, furanone), 1760 (C=O, coumaranone), 1665 (C=C, enol ether) cm^{-1}; MS (CI$^+$) 259 (M)$^+$, 97 [100%, (furanone)$^+$]. Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 65.02; H, 3.94.

Biological Activity. *Seeds.* Seeds of *Striga hermonthica* (Del.) Benth. and *Orobanche crenata* Forsk. were harvested in Sudan in 1987 and in Egypt in 1988, respectively, and were stored in the dark at room temperature until used in germination tests.

Preparation of Test Solutions. A compound to be tested was weighed out very accurately to the amount of 10 mg, dissolved in 10 mL of acetone P.A., and diluted with demineralized water to 100 mL. Aliquots of this stock solution were further diluted with water to obtain test solutions containing 1 and 0.01 mg/L test compound and 0.1 and 0.001% (v/v) acetone, respectively.

Bioassays. For surface sterilization seeds of *S. hermonthica* and *O. crenata* were exposed to an aqueous solution of sodium hypochlorite (2% active chlorine) and Triton X-100 (1% v/v) for 5 min with agitation. The seeds were then thoroughly rinsed with water and dried overnight.

For conditioning the sterilized seeds were spread on glass fiber filter paper disks (8-mm diameter; approximately 25–50 seeds per disk) in Petri dishes, wetted with water, and stored in the dark for 14 days at 23 °C for *Orobanche* seeds and at 27 °C for *Striga* seeds. Then the conditioning water was removed and replaced by 100 μL of test solution per disk. After incubation for another 4–7 days in the dark at indicated temperatures, the germination percentage was determined under a microscope. Seeds were considered to be germinated if the radical protruded through the seed coat.

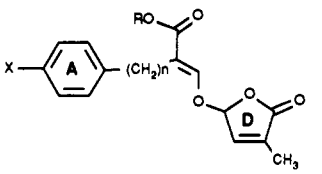
In each test series aqueous solutions with 0.1 and 0.001% (v/v) acetone were used as negative control. Test solutions of the stimulant GR24 (concentrations of 1 and 0.01 mg/L) were used as positive controls. Tests were replicated three times, and in each test the germination percentages were determined on at least 10 separate disks.

For full details of the bioassay, see Mangnus et al. (1992b).

RESULTS AND DISCUSSION

Strategy. In designing potential germination stimulants we used compound GR24, in which the A ring of strigol is replaced by an aromatic ring, as lead molecule. The bioactivity of GR24 is very high, and therefore, this change in the A ring of the natural molecule is acceptable for establishing a structure–activity relationship. In the design the D ring and its connecting oxymethylene unit were left intact, because it was found that changes in the D part of the strigol molecule are very critical with respect to the bioactivity (Hassanali, 1984; Mangnus and Zwanenburg, 1991).

The strategy of designing new structural modifications of GR24 is outlined in Scheme I. The underlying idea is to establish the influence of the rings B and C. By cutting the O_1–C_{8b} bond, analogue **6** arises in which ring C has been opened. By removing the C_4, analogue **7** comes out in which the B ring is no longer present. When both operations are performed at the same time, analogue **8** appears in which rings B and C are both lacking (Figure 2). For the sake of comparison some related compounds also lacking the B and C rings, **9**–**12**, were taken into consideration. Removal of atom C_8 from Johnson's analogue GR18 leads to compound **13**, another analogue lacking ring B and which is an isomer of **7** (Scheme II). To complete the series of compounds without ring B analogue **14**—in which rings A and C are fused—was also taken into consideration. The latter is isosteric to indolinone analogue **15** previously studied by Johnson et al. (1981) (Figure 3).



	n	X
8	2	H
9	1	H
10	0	H
11	0	Cl
12	0	OCH_3

Figure 2. AD ring analogues of GR24.

Synthesis. The synthetic design for this series of new strigol analogues is essentially the same for each compound, viz., α-formylation of a carboxylic ester or a γ-lactone with methyl formate, followed by coupling of the resulting enolate with a suitable furanone (see Scheme III). This coupling method has also been used to prepare GR24 and similar analogues (Johnson et al., 1981). The required starting materials which form the modified ABC part in the analogues **6**–**14** are all readily available. Methyl 2-indanylacetate (**21**) was prepared by hydrogenolysis and subsequent esterification of the tricyclic lactone **20** (ABC part of GR24), as depicted in Scheme IV. β- and γ-phenyl-γ-butyrolactone were obtained as a mixture from styrene oxide and diethyl malonate (De Puy et al., 1964) and subsequently separated by chromatography. (γ-Phenyl-γ-butyrolactone is also commercially available.) The starting carboxylic esters for analogues **8**–**12** were all obtained by esterification of the commercially available acids. 2-Coumaranone, the AC part of analogue **14**, is also commercially available.

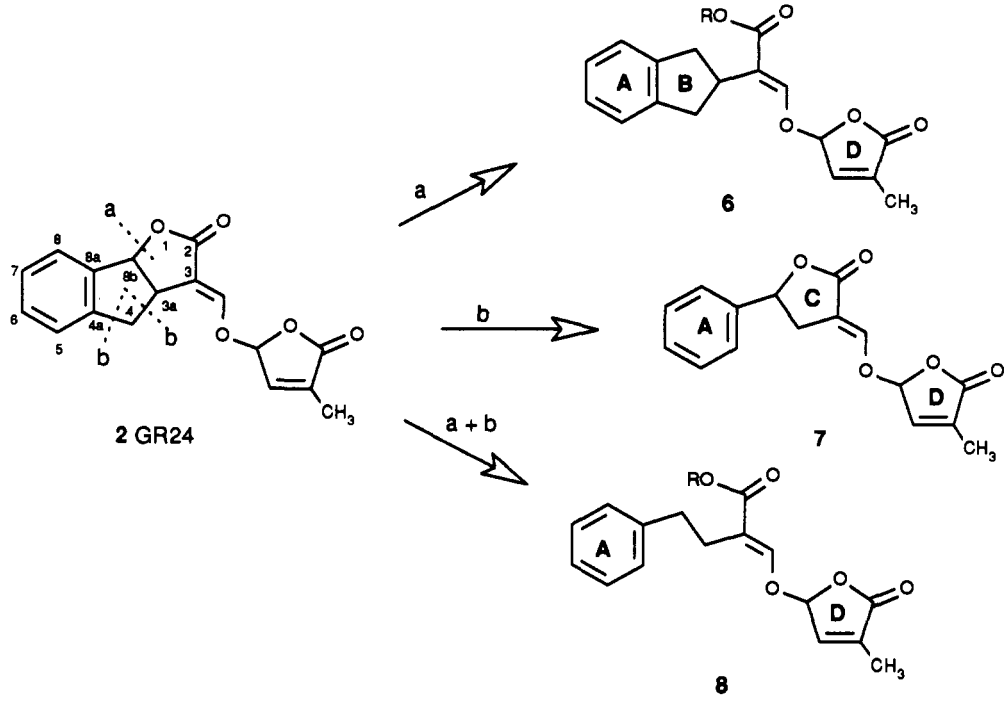
The coupling reactions were carried out as outlined in Scheme III, using potassium *tert*-butoxide as the base and bromofuranone **18** (L = Br) as D-ring precursor. Initially, it was attempted to isolate the intermediate hydroxymethylene compounds, but during the course of this study it was found that the highest yields are obtained when formylation and coupling of the enolate with bromofuranone are carried out in the same pot. A typical example is the preparation of analogue **7**: acidification of the intermediate potassium salt never afforded pure hydroxymethylene compound, but if formylation and coupling with **18** (L = Br) were combined in a one-pot procedure, the desired analogue **7** was obtained in 70% yield. Previously, attempts to isolate the free hydroxymethylene derivative of γ-butyrolactone revealed that in acidic solution retrocondensation gave unsubstituted γ-butyrolactone (Korte and Machleidt, 1955).

Analogues **8**, **9**, and **10** were obtained in increasing yields of 11, 23, and 68%, respectively, suggesting a strong influence of the aromatic ring on the formylation process. This effect was even more pronounced when it was attempted to isolate the intermediate hydroxymethylene compounds: yields 0, 31, and 78%, respectively.

Formylation of methyl 2-indanylacetate (**21**) could not be accomplished. This problem was overcome by first protecting the hydroxymethylene derivative of GR24 lactone. Subsequent hydrogenolysis followed by esterification and deprotection gave hydroxymethylene compound **25** in an overall yield of 32% (based on **22**, Scheme IV). Finally, coupling of **25** with bromofuranone **18** (L = Br) gave the desired analogue **6** in 52% yield.

Treatment of 2-coumaranone **26** with potassium *tert*-butoxide and methyl formate did not produce desired hydroxymethylene compound **29** but a dimer of 2-coumaranone **27** instead (Chatterjea, 1956). Therefore, first ethoxymethylene derivative **28** was prepared according to the method of Claisen (Bayer, 1954). Then, subsequent

Scheme I. Structural Modifications in the ABC Part of GR24



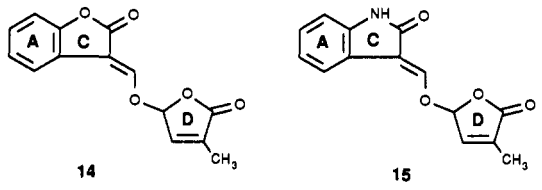
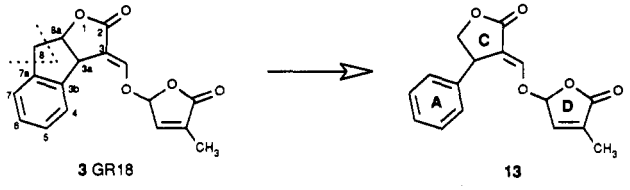


Figure 3. ACD ring analogues of GR24.

Scheme II. Structural Modification of GR18



hydrolysis gave hydroxymethylene compound **29** in 61% yield (based on **26**) (Scheme V). Coupling of **29** with bromofuranone **18** (L = Br) afforded the desired analogue **14** in low yield (16%).

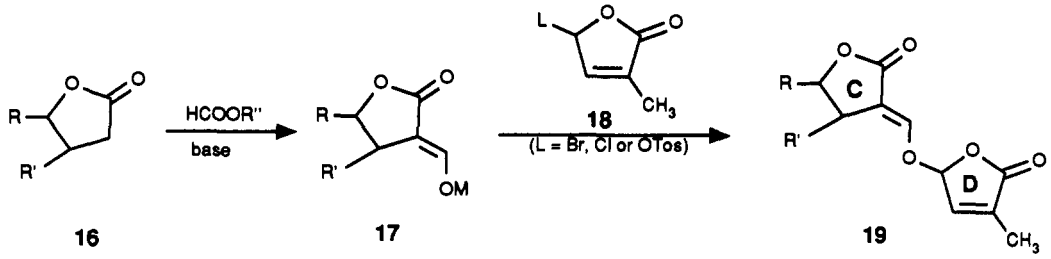
Biological Activity. The stimulatory activity of the GR24 analogues **6–14** was evaluated using seeds of *S. hermonthica* and *O. crenata*. The germination percentages are collected in Tables I and II together with those obtained with GR24 under the same conditions. The latter enables the comparison between results obtained in different test series, because the response of seeds of parasitic weeds, in particular of *S. hermonthica*, varied considerably from test to test. For the sake of comparison, also results obtained with Johnson's analogue GR5 are included in Tables I and II. For the evaluation of the bioactivity of compounds **7**, **13**, and GR24, mixtures of diastereomers were used, because at this stage we are not interested in the effect of stereochemistry.

The germination results reveal that all analogues, except compound **14**, are considerably active at the concentration of 1 mg/L. Relative to GR24 the percentages of germination observed for **6–13** and GR5 are not significantly different. This result demonstrates that the ABC part of GR24 (and strigol) is not a necessity for exhibiting stimulating activity. It therefore may be concluded that the actiphore for germination stimulation resides in the remaining part of the molecule, *viz.*, ring D, the enol ether linkage and ring C or its ester function. The precise role of each functional group in this actiphore still remains to be established, although it has been shown that the D ring alone is not active (Hassanali, 1984).

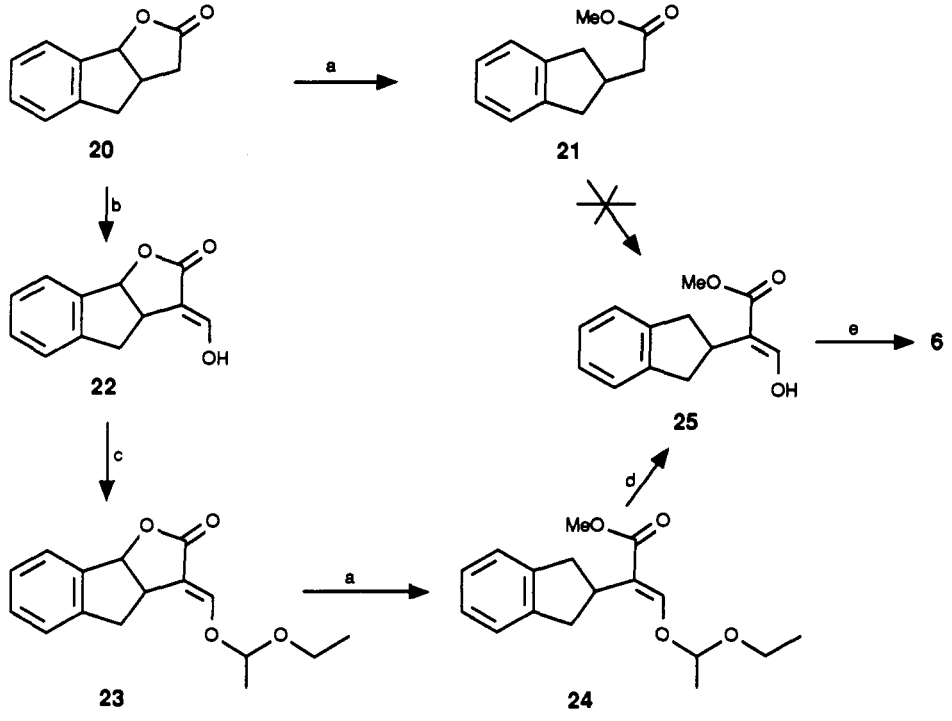
The effect of structural variations is much more pronounced when the results obtained with 0.01 mg/L stimulant are compared. Comparison of the bioactivity of compounds **6** and GR24 and of analogues **7** and **8** shows that there is a considerable decrease in activity when ring C is "opened" to a methyl ester. The effect of the presence of ring B on the bioactivity is deduced from a comparison of the activity of compounds **7** and GR24 and of **6** and **8**. Clearly, the effect of the presence of ring B is much less pronounced than that of ring C. Comparison of the activities of analogues **7** and **13** on one hand with that of GR5 on the other hand clearly demonstrates that the presence of ring A enhances the stimulatory activity to a considerable extent. The germination activity observed for *O. crenata* seeds at a concentration level of 0.01 mg/L are rather low, and therefore the conclusions mentioned above are less well substantiated.

The overall conclusion is that a closer resemblance with the structure of the GR24 molecule corresponds with a higher bioactivity. It is therefore suggested that the ABC part of GR24 plays an important role in the attachment of the molecule to the receptor site. Apparently, the rigid configuration of the ABC part of GR24 ensures an efficient interaction with the receptor site. Opening of ring C allows free rotation around the C_2–C_3 and C_3–C_{3a} bonds of GR24-type structures, and as a consequence spatial arrangements of the molecule that are very different from that of GR24 become energetically more attractive. Hence, the conformation resembling GR24, which is needed to ensure an effective binding to the receptor site, is only present to a minor extent and accordingly the stimulating activity will be reduced. When, on the other hand, ring B is opened, only one extra possibility for free rotation, *viz.*, the bond between A and C ring, is introduced, which apparently has no large effect on the bioactivity.

Scheme III. Strategy for the Synthesis of Strigol Analogues

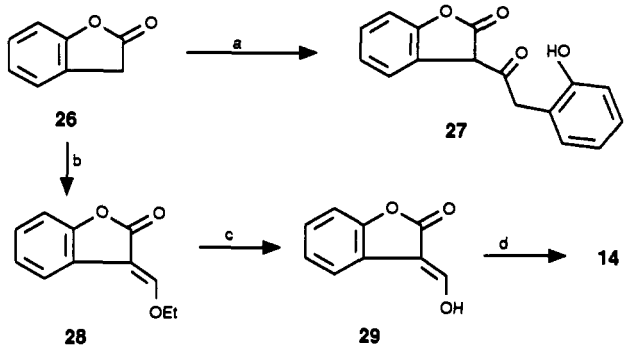


Scheme IV. Synthesis of Analogue 6



[a] 1. H_2, Pd/C, MeOH. 2. CH_2N_2, MeOH. [b] 1. KOtBu, HCOOMe, THF. 2. H^+. [c] ethyl vinyl ether, pTosOH. [d] 0.5N HCl, THF. [e] KOtBu, bromobutenolide 18 (L =,Br).

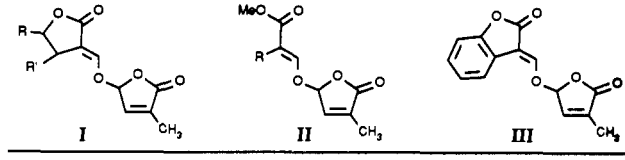
Scheme V. Synthesis of Analogue 14



[a] KOtBu, HCOOMe, THF. [b] $HC(OEt)_3$, $(MeCO)_2O$, Δ. [c] HOAc / HCl. [d] KOtBu, 18 (L = Br).

Variations in the positions of ring A with respect to the actiphore also demonstrate that the ABC part plays an important role in the attachment of the stimulant to the receptor site. If the A ring can no longer approximate its original position as in the GR24 molecule, the germination stimulant activity is reduced, which is evident from a comparison of the germination percentages of analogue 10 with those of 8 and 9 (at the concentration level of 1 mg/L for seeds of *S. hermonthica* as well as *O. crenata*). The difference between 8 and 9 is not very large, meaning that in both compounds the A ring can adopt an acceptable spatial position. This also explains the difference in bio-

Table I. Germination Percentages for Seeds of *S. hermonthica* after Exposure to Solutions of Strigol Analogues at Concentrations of 1 and 0.01 mg/L[a]

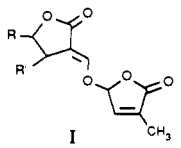


sample		% germination ± $t_{0.05}(s/n^{1/2})$ at	
no.	structure	1 mg/l	0.01 mg/L
6	II, R = indanyl	46.2 ± 4.2 (46.7 ± 3.9)[b]	10.1 ± 2.1 (48.3 ± 4.9)[b]
7	I, R = Ph, R′ = H	46.9 ± 6.5 (55.1 ± 6.7)[b]	51.1 ± 6.8 (61.1 ± 5.1)[b]
8	II, R = CH_2CH_2Ph	32.7 ± 3.7 (36.8 ± 4.3)[b]	3.0 ± 1.2[c] (42.4 ± 5.1)[b]
9	II, R = CH_2Ph	41.9 ± 3.0 (49.5 ± 3.7)[b]	3.9 ± 1.0[c] (52.5 ± 3.6)[b]
10	II, R = Ph	29.3 ± 3.0 (44.4 ± 3.4)[b]	1.9 ± 0.6[c] (47.6 ± 3.2)[b]
11	II, R = Ph(pCl)	21.9 ± 5.2 (29.5 ± 5.3)[b]	7.9 ± 2.0 (35.9 ± 4.7)[b]
12	II, R = Ph(pOMe)	24.4 ± 4.4 (29.5 ± 5.3)[b]	2.5 ± 1.3[c] (35.9 ± 4.7)[b]
13	I, R = H, R′ = Ph	49.1 ± 5.6 (55.1 ± 6.7)[b]	26.8 ± 5.2 (61.1 ± 5.1)[b]
14	III	5.0 ± 1.9[c] (26.9 ± 5.2)[b]	3.1 ± 1.7[c] (33.9 ± 4.6)[b]
GR5	I, R = R′ = H	43.2 ± 7.0 (44.5 ± 5.8)[b]	1.6 ± 0.6[c] (45.6 ± 6.7)[b]

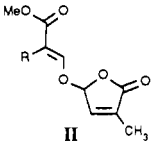
[a] Germination percentages given are the mean of two replicate tests. In each test the percentage was determined 10 times by counting the number of germinated *Striga* seeds in a sample of 25 seeds. [b] The values in parentheses are the mean germination percentages for seeds tested under the same conditions and at the same time, with GR24 as stimulant. [c] Values are not significantly different from germination percentages obtained in the control (without stimulant).

activity between 7 and 13 at the 0.01 mg/L level for both seed species.

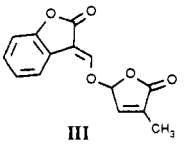
Table II. Germination Percentages for Seeds of *O. crenata* after Exposure to Solutions of Strigol Analogues at Concentrations of 1 and 0.01 mg/L[a]



I



II



III

sample		% germination ± $t_{0.05}(s/n^{1/2})$ at	
no.	structure	1 mg/L	0.01 mg/L
6	II, R = indanyl	65.5 ± 2.6 (64.6 ± 2.8)[b]	1.4 ± 0.6 (7.9 ± 1.2)[b]
7	I, R = Ph, R′ = H	83.7 ± 3.0 (83.8 ± 2.9)[b]	13.6 ± 2.1 (17.7 ± 2.5)[b]
8	II, R = CH_2CH_2Ph	55.9 ± 3.1 (66.6 ± 3.0)[b]	0.4 ± 0.4[c] (11.1 ± 1.9)[b]
9	II, R = CH_2Ph	62.8 ● 2.6 (69.9 ± 2.2)[b]	4.0 ± 0.9 (10.7 ± 1.2)[b]
10	II, R = PH	41.5 ± 1.9 (69.3 ± 2.0)[b]	0.3 ± 0.2[c] (11.8 ± 1.2)[b]
11	II, R = Ph(pCl)	58.8 ± 4.2 (66.9 ± 4.3)[b]	1.7 ± 1.3 (15.3 ± 2.5)[b]
12	II, R = Ph(pOMe)	48.4 ± 3.7 (66.9 ± 4.3)[b]	0.7 ± 0.7[c] (15.3 ± 2.5)[b]
13	I, R = H, R′ = Ph	79.6 ± 2.4 (83.8 ± 2.9)[b]	5.1 ± 1.4 (17.7 ± 2.5)[b]
14	III	0.9 ± 0.5[c] (72.0 ± 3.1)[b]	0.1 ± 0.2[c] (17.7 ± 2.2)[b]
GR5	I, R = R′ = H	30.7 ± 3.7 (73.2 ± 3.1)[b]	0.4 ± 0.4[c] (25.5 ± 2.4)[b]

[a] Germination percentages given are the mean of two replicate tests. In each test the percentage was determined 10 times by counting the number of germinated *Striga* seeds in a sample of 25 seeds. [b] The values in parentheses are the mean germination percentages for seeds tested under the same conditions and at the same time, with GR24 as stimulant. [c] Values are not significantly different from germination percentages obtained in the control (without stimulant).

Compound **14** can be considered as a modification of analogue **10** in which the ester function is "closed" to ring C. Thus, it was expected that **14** would exhibit an activity at least as good as that of analogue **10**. However, compound **14** was found to be completely inactive. To explain this unexpected observation, the following possibilities can be conceived. First, the bicyclic part of **14** has a planar structure in contrast to all ABC-ring analogues which have a bend structure. Nevertheless, in view of the activity of GR5 and GR7, at least some activity of **14** was anticipated. A second explanation for the loss of activity of **14** involves electronic interactions between the aromatic ring and the *exo*-methylene moiety. This explanation is unlikely, because similar conjugative effects are present in analogues **10–12**, which were found to be appreciably active. Third, the lack of activity may be attributed to high susceptibility of the ring C in **14** toward hydrolysis, which leads to free acids prior to interaction with the receptor site. Indirect evidence for this suggestion is provided by the observation that formylation of 2-coumaranone with base and methyl formate results in the formation of dimer **27** (Scheme V). Moreover, preliminary results of a related study show that free acids are inactive in spite of a high activity for their corresponding esters (unpublished results).

Comparison of the activities of **10–12** reveals that substitution of the aromatic ring hardly affects the bioactivity. Only the *p*-chloro compound **11** is slightly more active at the concentration level of 0.01 mg/L; however, the enhanced activity is of marginal significance.

Conclusion. From a synthetic point of view the present study demonstrates that α-formylation of γ-lactones is less complicated than α-formylation of the corresponding aliphatic esters.

Tests of biological activity of stimulants in the concentration range 10^{-6}–10^{-8} M suggest that the tricyclic ABC part of GR24 (and strigol) is not essential for the activity as germination stimulant but that this part of the molecule determines the spatial conformation of the molecule and in this manner determines the interaction with the receptor site. When more rotational freedom is introduced in the GR24 analogues, by opening of ring C or at a lesser extent by opening of ring B, the bioactivity is negatively influenced, particularly at lower concentrations of stimulant. It was also shown that the simple analogue **7** approximates the bioactivity of GR24, but its synthesis is far less complicated. The tricyclic ABC part requires a five-step synthesis from 1-indanone, whereas the γ-phenyl-γ-butyrolactone is commercially available. Therefore, **7**, which is also very active on *Striga asiatica* seeds (Brooks et al., 1987), is an attractive alternative for GR24 and should be further investigated as potential control agent for parasitic weeds, of the genera *Striga* and *Orobanche*.

ACKNOWLEDGMENT

We thank A. G. T. Babiker and O. A. Al-Menoufi for supplying *Striga* and *Orobanche* seeds and H. Amatdjais and P. v. Galen for conducting analysis and mass measurements. We gratefully acknowledge the Commission of the European Communities for financial support.

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Received for review October 22, 1991. Revised manuscript received February 29, 1992. Accepted March 26, 1992.

Registry No. 1, 11017-56-4; 2, 76974-79-3; 6 (R = CH_3), 141250-17-1; (±)-7 (isomer 1), 141250-18-2; (±)-7 (isomer 2), 141271-78-5; (±)-8 (R = CH_3), 141250-19-3; (±)-9, 141250-20-6; (±)-10, 141250-21-7; (±)-11, 141250-22-8; (±)-12, 141250-23-9; (±)-13 (isomer 1), 141250-24-0; (±)-13 (isomer 2), 141250-25-1; (±)-14, 141250-26-2; (±)-16 (R = Ph, R′ = H), 69814-97-7; (±)-16 (R = H, R′ = Ph), 93601-84-4; (±)-17 (R = H, R′ = Ph, M = H), 141250-27-3; (±)-18 (L = Br), 59488-94-7; 20, 4471-33-4; 21, 53273-37-3; 22, 141317-42-2; 23, 141250-28-4; 24, 141250-29-5; 25, 141250-30-8; 26, 553-86-6; 28, 141250-31-9; 29, 141250-32-0; 2-indanylacetic acid, 37868-26-1; (*E*)-methyl 2-(hydroxymethylene)-3-phenylpropanoate, 108179-22-2; methyl formate, 107-31-3; methyl 4-phenylbutyrate, 2046-17-5; methyl 3-phenylpropanoate, 103-25-3; methyl phenylacetate, 101-41-7; methyl 4-chlorophenylacetate, 52449-43-1; methyl 4-methoxyphenylacetate, 23786-14-3; triethyl formate, 122-51-0.